ANNEX

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cetrotide 0.25 mg powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial contains:
0.26 - 0.27 mg cetrorelix acetate equivalent to 0.25 mg cetrorelix.

After reconstitution with the solvent provided, the concentration of cetrorelix is 0.25 mg/ml.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of premature ovulation in patients undergoing a controlled ovarian stimulation, followed by oocyte pick-up and assisted reproductive techniques.

In clinical trials Cetrotide 0.25 mg was used with human menopausal gonadotropin (HMG), however, limited experience with recombinant FSH suggested similar efficacy.

4.2 Posology and method of administration

Cetrotide 0.25 mg should only be prescribed by a specialist experienced in this field.

Cetrotide 0.25 mg is for subcutaneous injection into the lower abdominal wall.

The first administration of Cetrotide should be performed under the supervision of a physician and under conditions where treatment of possible pseudo-allergic reactions is immediately available. The following injections may be self-administered as long as the patient is made aware of the signs and symptoms that may indicate hypersensitivity, the consequences of such a reaction and the need for immediate medical intervention.

The contents of 1 vial (0.25 mg cetrorelix) are to be administered once daily, at 24 h intervals, either in the morning or in the evening. Following the first administration, it is advised that the patient be kept under medical supervision for 30 minutes to ensure there is no allergic/pseudo-allergic reaction to the injection. Facilities for the treatment of such reactions should be immediately available.

Administration in the morning: Treatment with Cetrotide 0.25 mg should commence on day 5 or 6 of ovarian stimulation (approximately 96 to 120 hours after start of ovarian stimulation) with urinary or recombinant gonadotropins and is to be continued throughout the gonadotropin treatment period including the day of ovulation induction.

Administration in the evening: Treatment with Cetrotide 0.25 mg should commence on day 5 of ovarian stimulation (approximately 96 to 108 hours after start of ovarian stimulation) with urinary or recombinant gonadotropins and is to be continued throughout the gonadotropin treatment period until the evening prior to the day of ovulation induction.

For instructions for use and handling, see section 6.6.

4.3 Contraindications

- Hypersensitivity to cetrorelix acetate or any structural analogues of GnRH, extrinsic peptide hormones or mannitol.
- Pregnancy and lactation.
- Postmenopausal women.
- Patients with moderate and severe renal and hepatic impairment.

4.4 Special warnings and special precautions for use

Special care should be taken in women with signs and symptoms of active allergic conditions or known history of allergic predisposition. Treatment with Cetrotide is not advised in women with severe allergic conditions.

During or following ovarian stimulation an ovarian hyperstimulation syndrome can occur. This event must be considered as an intrinsic risk of the stimulation procedure with gonadotropins.

An ovarian hyperstimulation syndrome should be treated symptomatically, e.g. with rest, intravenous electrolytes/colloids and heparin therapy.

Luteal phase support should be given according to the reproductive medical centre´s practice.

There is limited experience up to now with the administration of Cetrotide 0.25 mg during a repeated ovarian stimulation procedure. Therefore Cetrotide 0.25 mg should be used in repeated cycles only after a careful risk/benefit evaluation.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro investigations have shown that interactions are unlikely with medications that are metabolised by cytochrome P450 or glucuronised or conjugated in some other way. However, the possibility of interactions with commonly used medicinal products cannot entirely be excluded.

4.6 Pregnancy and lactation

Cetrotide 0.25 mg is not intended to be used during pregnancy and lactation (see section 4.3 “Contra-indications“).

Studies in animals have indicated that cetrorelix exerts a dose related influence on fertility, reproductive performance and pregnancy. No teratogenic effects occurred when the drug was administered during the sensitive phase of gestation.

4.7 Effects on ability to drive and use machines

Due to its pharmacological profile cetrorelix is unlikely to impair the patient’s ability to drive or to operate machinery.

4.8 Undesirable effects

Local reactions at the injection site (e.g. erythema, swelling and pruritus) have been reported. Usually they were transient in nature and mild intensity. The frequency as reported in clinical trials was 9.4% following multiple injections of 0.25 mg cetrorelix. Rare cases of hypersensitivity reactions including pseudo-allergic/anaphylactoid reactions have also been reported.

Occasionally nausea and headache have been reported.

Occasionally an ovarian hyperstimulation syndrome can occur which is an intrinsic risk of the stimulation procedure (see section 4.4 “Special warnings and precautions for use”).

4.9 Overdose

Overdosage in humans may result in a prolonged duration of action but is unlikely to be associated with acute toxic effects.

In acute toxicity studies in rodents non-specific toxic symptoms were observed after intraperitoneal administration of cetrorelix doses more than 200 times higher than the pharmacologically effective dose after subcutaneous administration.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: LHRH-Antagonist, ATC code: H01CC02.

Cetrorelix is a luteinising hormone releasing hormone (LHRH) antagonist. LHRH binds to membrane receptors on pituitary cells. Cetrorelix competes with the binding of endogenous LHRH to these receptors. Due to this mode of action, cetrorelix controls the secretion of gonadotropins (LH and FSH).

Cetrorelix dose-dependently inhibits the secretion of LH and FSH from the pituitary gland. The onset of suppression is virtually immediate and is maintained by continuous treatment, without initial stimulatory effect.

In females, cetrorelix delays the LH surge and consequently ovulation. In women undergoing ovarian stimulation the duration of action of cetrorelix is dose dependent. Following a single dose of 3 mg of cetrorelix a duration of action of at least 4 days has been evaluated. On day 4 the suppression was approximately 70%. At a dose of 0.25 mg per injection repeated injections every 24 hours will maintain the effect of cetrorelix.

In animals as well as in humans, the antagonistic hormonal effects of cetrorelix were fully reversible after termination of treatment.

5.2 Pharmacokinetic properties

The absolute bioavailability of cetrorelix after subcutaneous administration is about 85%.

The total plasma clearance and the renal clearance are 1.2 ml x min^{-1} x kg^{-1} and 0.1 ml x min^{-1} x kg^{-1} , respectively. The volume of distribution ($V_{d,area}$) is 1.1 l x kg^{-1}. The mean terminal half-lives following intravenous and subcutaneous administration are about 12 h and 30 h, respectively, demonstrating the effect of absorption processes at the injection site. The subcutaneous administration of single doses (0.25 mg to 3 mg cetrorelix) and also daily dosing over 14 days show linear kinetics.

5.3 Preclinical safety data

No target organ toxicity could be observed from acute, subacute and chronic toxicity studies in rats and dogs following subcutaneous administration of cetrorelix. No signs of drug-related local irritation or incompatibility were noted in dogs after intravenous, intra-arterial and paravenous injection when cetrorelix was administered in doses clearly above the intended clinical use in man.

Cetrorelix showed no mutagenic or clastogenic potential in gene and chromosome mutation assays.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, water for injections

6.2 Incompatibilities

As cetrorelix is incompatible with several substances of common parenteral solutions it should be dissolved only by using water for injections.

6.3 Shelf life

2 years.

The solution should be used immediately after preparation.

6.4 Special precautions for storage

Do not store above 25 °C. Keep the container in the outer carton.

6.5 Nature and contents of container

Packs with 1 or 7 Type I glass vials each containing 55.7 mg powder for solution for injection sealed with a rubber stopper.

Additionally for each vial the packs contain:

1 pre-filled syringe (Type I glass cartridge closed with rubber stoppers) with 1 ml solvent for parenteral use
1 injection needle (20 gauge)
1 hypodermic injection needle (27 gauge)
2 alcohol swabs.

6.6 Instructions for use, handling, and disposal

Cetrotide 0.25 mg should only be reconstituted with the solvent provided, using a gentle, swirling motion. Vigorous shaking with bubble formation should be avoided.

Do not use if the solution contains particles or if the solution is not clear.

Withdraw the entire contents of the vial. This ensures a delivery to the patient of a dose of at least 0.23 mg cetrorelix.

The solution should be used immediately after reconstitution.

The injection site should be varied daily.

7. MARKETING AUTHORISATION HOLDER

Serono Europe Limited
56 Marsh Wall
London E14 9TP
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/100/001
EU/1/99/100/002

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

13 April 1999

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Cetrotide 3 mg powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial contains:
3.12 - 3.24 mg cetrorelix acetate equivalent to 3 mg cetrorelix.

After reconstitution with the solvent provided, the concentration of cetrorelix is 1 mg/ml.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of premature ovulation in patients undergoing a controlled ovarian stimulation, followed by oocyte pick-up and assisted reproductive techniques.

In clinical trials Cetrotide 3 mg was used with human menopausal gonadotropin (HMG), however, limited experience with recombinant FSH suggested similar efficacy.

4.2 Posology and method of administration

Cetrotide 3 mg should only be prescribed by a specialist experienced in this field.

Cetrotide 3 mg is for subcutaneous injection into the lower abdominal wall.

The first administration of Cetrotide should be performed under the supervision of a physician and under conditions where treatment of possible pseudo-allergic reactions is immediately available. The following injections may be self-administered as long as the patient is made aware of the signs and symptoms that may indicate hypersensitivity, the consequences of such a reaction and the need for immediate medical intervention.

The contents of 1 vial (3 mg cetrorelix) are to be administered on day 7 of ovarian stimulation (approximately 132 to 144 hours after start of ovarian stimulation) with urinary or recombinant gonadotropins. Following the first administration, it is advised that the patient be kept under medical supervision for 30 minutes to ensure there is no allergic/pseudo-allergic reaction reaction to the injection. Facilities for the treatment of such reactions should be immediately available.

If the follicle growth does not allow ovulation induction on the fifth day after injection of Cetrotide 3 mg, additionally 0.25 mg cetrorelix (Cetrotide 0.25 mg) should be administered once daily beginning 96 hours after the injection of Cetrotide 3 mg until the day of ovulation induction.

For instructions for use and handling, see section 6.6.

4.3 Contraindications

- Hypersensitivity to cetrorelix acetate or any structural analogue of GnRH, extrinsic peptide hormones or mannitol.
- Pregnancy, and lactation.
- Postmenopausal women.
- Patients with moderate and severe renal and hepatic impairment.

4.4 Special warnings and special precautions for use

Special care should be taken in women with signs and symptoms of active allergic conditions or known history of allergic predisposition. Treatment with Cetrotide is not advised in women with severe allergic conditions.

During or following ovarian stimulation an ovarian hyperstimulation syndrome can occur. This event must be considered as an intrinsic risk of the stimulation procedure with gonadotropins.

An ovarian hyperstimulation syndrome should be treated symptomatically, e.g. with rest, intravenous electrolytes/colloids and heparin therapy.

Luteal phase support should be given according to the reproductive medical centre´s practice.

There is limited experience up to now with the administration of Cetrotide 3 mg during a repeated ovarian stimulation procedure. Therefore Cetrotide 3 mg should be used in repeated cycles only after a careful risk/benefit evaluation.

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Occasionally nausea and headache have been reported.

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Overdosage in humans may result in a prolonged duration of action but is unlikely to be associated with acute toxic effects.

In acute toxicity studies in rodents non-specific toxic symptoms were observed after intraperitoneal administration of cetrorelix doses more than 200 times higher than the pharmacologically effective dose after subcutaneous administration.

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Cetrorelix dose-dependently inhibits the secretion of LH and FSH from the pituitary gland. The onset of suppression is virtually immediate and is maintained by continuous treatment, without initial stimulatory effect.

In females, cetrorelix delays the LH surge and consequently ovulation.

In women undergoing ovarian stimulation the duration of action of cetrorelix is dose dependent. Following a single dose of 3 mg of cetrorelix a duration of action of at least 4 days has been evaluated. On day 4 the suppression was approximately 70%. At a dose of 0.25 mg per injection repeated injections every 24 hours will maintain the effect of cetrorelix.

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6.2 Incompatibilities

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6.3 Shelf life

2 years.

The solution should be used immediately after preparation.

6.4 Special precautions for storage

Do not store above 25 °C. Keep the container in the outer carton.

6.5 Nature and contents of container

Pack with 1 Type I glass vial containing 167.7 mg powder for solution for injection sealed with a rubber stopper.

Additionally the pack contains:

1 pre-filled syringe (Type I glass cartridge closed with rubber stoppers) with 3 ml solvent for parenteral use
1 injection needle (20 gauge)
1 hypodermic injection needle (27 gauge)
2 alcohol swabs.

6.6 Instructions for use, handling, and disposal

Cetrotide 3 mg should only be reconstituted with the solvent provided, using a gentle, swirling motion. Vigorous shaking with bubble formation should be avoided.

Do not use if the solution contains particles or if the solution is not clear.

Withdraw the entire contents of the vial. This ensures a delivery to the patient of a dose of at least 2.82 mg cetrorelix.

The solution should be used immediately after reconstitution.

7. MARKETING AUTHORISATION HOLDER

Serono Europe Limited
56 Marsh Wall
London E14 9TP
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/100/003

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